

U.S.S.N. 10/044,538

Filed: January 10, 2002

## AMENDMENT AND RESPONSE TO OFFICE ACTION

## Remarks

Claims 1-26 are pending. Claims 1, 2, 4, 5, 10, and 21 have been amended. Claims 25 and 26 have been added. It appears that applicants paid for a total of 26 claims when the application was originally filed even though only 24 claims were present. Thus, applicants believe that a fee for the two added claims is not needed at this time. However, should a fee be required, the Commissioner is authorized to charge the fee to Deposit Account No. 50-3129.

The present application discloses polycationic polysaccharide derivatives prepared from the conjugation of oligoamines onto a polysaccharide chain, wherein the oligoamine conjugated polysaccharide further comprises hydrophobic or amphiphilic groups grafted covalently to the polymer chain. The oligoamines, having at least two amino groups, are conjugated with at least one oligomer per five saccharide units. The hydrophobic groups can be saturated or unsaturated hydrocarbons derived from, for example, natural and synthetic fatty acids, cholesterol derivatives, or aromatic groups such as naphthyl and benzyl groups. The hydrophobic and amphiphilic groups are positioned with at least one group per 50 saccharide units.

Claim 1 is amended to define the polysaccharides as natural or synthetic polysaccharides. Support for the amendment is found, for example, at page 12, lines 2-4 and page 14, lines 10-13. Further, claim 1 is amended to recite a polysaccharide *compound* in view of the Examiner's comments.

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Claim 4 is amended to recite dextrans, alginates, and their derivatives provided the polysaccharide chains have an amount of saccharide ranging from 2 to 2000 units. Support for the amendment is found, for example, at page 15, lines 7-17.

Claim 5 is amended to recite that the saccharide units in a synthetic polysaccharide are connected by an acetal, hemiacetal, ketal, orthoester, amide, ester, carbonate or carbamate bond. Support for the amendment is found, for example, at page 9, lines 4-9 of the specification.

Claim 10 is amended to recite that the oligoamine is either spermine or alkyl-substituted spermine, wherein the alkyl substituent contains 1-6 carbons. Support for the amendment is found, for example, at page 9, lines 16-17.

Claims 23 and 24 have been amended to more clearly define compositions for use in tissue engineering and electronic circuit design. Support for the amendments is found, for example, on page 54, lines 18-27.

**Rejection Under 35 U.S.C. § 112, second paragraph**

Claims 1 and 4-20 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary skill in the pertinent art at the

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time the invention was made. The test for definiteness under 35 U.S.C. 112, second paragraph is whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. (*Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)).

Claim 4 has been amended to more clearly define the members of the Markush group. The Examiner stated that the recitations "dextrans" and "alginates" are seen to include derivatives, which have not been particularly pointed out or distinctly claimed and therefore the metes and bounds of the derivatives cannot be sufficiently determined. One of ordinary skill in the art would recognize that the terms "dextrans" and "alginates" refer to dextran and alginate polymers of different molecular weights, i.e. different number of saccharide monomer units. The applicant discloses that the polysaccharide must contain between 2 and 2000 saccharide units.

The Examiner states that claim 5 is unclear because the saccharide units in a polysaccharide are generally connected via ether linkages. Claim 5 has been amended to recite *synthetic* polysaccharides, in which the saccharide units can be connected by a linkage other than an ether linkage.

The Examiner states that the recitation "a spermine" in claim 10 includes derivatives of spermine and that it is unclear what derivatives are intended. Claim 10 has been amended to recite an oligoamine selected from the group consisting of spermine or alkyl-substituted spermine, wherein the alkyl substituent contains 1-6 carbons. As a result, the metes and bounds of the derivatives can be determined by one of ordinary skill in the art.

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The Examiner has maintained the rejection of claim 12. Specifically, the Examiner contends that the term "oligomer" is indefinite because it is not clear if said term is intended to mean different sizes of polymers. In addition, the Examiner argues that the term "cholesterols" includes derivatives of cholesterol and is therefore indefinite because the applicant does not claim specific derivatives of cholesterol.

An oligomer is defined as a molecule of intermediate relative molecular mass, the structure of which essentially comprises a small plurality of units derived, actually or conceptually, from molecules of lower relative molecular mass (IUPAC Recommendations on Nomenclature, 1996). The applicant discloses a biodegradable polycation composition having an amphiphilic residue wherein the amphiphilic residue is selected from the group consisting of fatty chains, phospholipids, cholesterol, ethylene glycol oligomers, propylene glycol oligomers and combinations thereof. One of ordinary skill in the art would recognize that the terms "ethylene glycol oligomers" and "propylene glycol oligomers" refer to polymers of ethylene and propylene glycol comprising a small number (i.e. 2 to 10) of monomer units.

Claim 12 also refers to "cholesterols", which one of ordinary skill in the art would understand to mean cholesterol and derivatives thereof. For example, in Example 8 on page 45, line 28, the specification teaches the conjugation of cholesterol to hydrophilic polysaccharides. In addition, on pages 23 and 26, the specification discloses a number of derivatives of cholesterol, including Cholesteryl chloroformate, Cholesteric acid N-hydroxy succinimide (NHS) ester, di-Chol-L-Lysine-NHS, and di-Chol-L-Lysine-OMe. Furthermore, a number of

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papers disclosing cholesterol derivatives were published well before the filing of the current application (see, for example, Farhood H et al., "Effect of cationic cholesterol derivatives on gene transfer and protein kinase C activity" in *Biochim Biophys Acta*. 1111(2):239-46 (1992) and Vigneron JP et al., "Guanidinium-cholesterol cationic lipids: efficient vectors for the transfection of eukaryotic cells" in *Proc. Natl. Acad. Sci. USA* 93(18):9682-6 (1996), copies of which were enclosed with the amendment and response mailed on January 21, 2004). Therefore, one of ordinary skill in the art would understand what is claimed by the applicants when the claim is read in light of the specification.

**Rejection Under 35 U.S.C. § 102**

Claims 1, 4, 5, 7, 12, 14, 16-21, 23, and 24 were rejected under 35 U.S.C. § 102(b) as being anticipated by European Patent No. 0370810 to Yamaguchi et al. ("Yamaguchi"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Yamaguchi discloses fatty emulsions stabilized by polysaccharide derivatives which can embed fat-soluble substances for use in medicine, food and the like (page 2, lines 3-5). The polysaccharide derivatives described are preferably substituted by  $-OCH_2CONHCH_2CH_2NHR$  wherein R is hydrogen or a cholesteryloxycarbonyl group at a proportion of 0.5 to 3 per 100

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sugar units (page 2, lines 53-56). The polysaccharide derivative is preferably a pullulan, amylopectin, amylose, dextrin, cyclodextrin, dextran, hydroxyethyl dextran, or mannan and is more preferably N-[2-(cholesteryloxycarbonylamino)-ethyl]carbamoylmethylated pullulan (page 2, lines 32-33, lines 47-48).

The ethylene diamine linker disclosed by Yamaguchi does not contain at least two amine groups. Rather, it contains an amine ( $-\text{CH}_2\text{NHR}$ ) and an amide group ( $-\text{CONHCH}_2$ ) (page 2, lines 53-56). An amide group is an amine adjacent to a carbonyl ( $\text{C}=\text{O}$ ) group. Such a moiety is not basic and therefore would not form a cation under physiological conditions. As a result, there is only a single amine group capable of forming a cation under physiological conditions. Accordingly, the claims of the present application are not anticipated by Yamaguchi.

When, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated if one of them is in the prior art. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (citing *In re Petering*, 301 F.2d 676, 682, 133 USPQ 275, 780 (CCPA 1962)). The Examiner asserts that Yamaguchi discloses a polysaccharide substituted with an oligoamine containing at least two amino groups and that this group is substituted at a proportion of 0.5 to three per 100 saccharide units, which corresponds to 0.25 to 1.5 per 50 sugar units. As was discussed above, Yamaguchi does not disclose a polysaccharide substituted with an oligoamine containing at least two amino groups. However, even if one could argue that the oligoamines disclosed by Yamaguchi contain at least two *amino* groups, the oligoamines are not present in a proportion which would anticipate the claims of the present application. The

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applicants disclose that the oligoamines in the present application must be present in a minimum ratio of 1 per 5 sugar units (page 8, lines 5-9), which corresponds to *at least 20 oligoamines per 100 saccharide units*. Such a proportion is outside the range disclosed by Yamaguchi.

Therefore, the claims of the present application are not anticipated by Yamaguchi.

Finally, the Examiner states that the compositions described by Yamaguchi contain an  $-OCH_2$  group, which connects the oligoamine and the cholesterol group, and thus satisfies the limitations of claim 18 in the present application. Claim 18 is directed to a biodegradable polycation composition according to claim 1, wherein the compositions further comprises a ligand for facilitating the binding of said composition to a cell or tissue. The applicants disclose that the efficiency of gene delivery can be enhanced by the addition of protein ligands that can be covalently coupled to the polymer and then incorporated into a ligand-nucleic acid complex (page 16, 3-11). The resulting complexes can interact specifically with cognate receptors on the target cell. Accordingly, Yamaguchi does not disclose the addition of protein ligands covalently coupled to the polymer and then incorporated into a ligand-nucleic acid complex in order to enhance gene delivery.

**Double Patenting Rejection**

Claims 1-24 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 10/031,728 ("the '728 application"). The Examiner alleges that claim 1 of the

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copending '728 application is drawn to the same polycation composition as claim 1 of the present application. Applicants respectfully traverse this rejection.

Claim 1 of the present application recites a polycation complex comprising a polysaccharide, at least one oligoamine grafted to the polysaccharide, and at least one further grafted group which is either a hydrophobic or an amphiphilic group which is grafted to the polysaccharide chain. Claim 2 of the present application is drawn to a biodegradable polycation complex with a polyanion comprising a polysaccharide, at least one oligoamine grafted to the polysaccharide, and at least one further grafted group which is either a hydrophobic or an amphiphilic group which is grafted to the polysaccharide chain.

Claims 1-19 of the '728 application recites a biodegradable polycation composition associated with an anionic macromolecule comprising a *linear* polysaccharide and at least one oligoamine directly grafted to the linear polysaccharide and wherein the oligoamine has a *molecular weight of up to 2000 Daltons*.

Claims 1-19 of the '728 application do not recite a polycation complex comprising hydrophobic or amphiphilic groups attached to the polysaccharide chain in a density of one per 50 saccharide units and wherein the hydrophobic or amphiphilic group includes an aliphatic chain of 1-4 carbons. Further, claim 1 of the '728 application includes the limitations that the polysaccharide chain must be *linear* and that the oligoamine has a molecular weight up to 2000 Daltons. These limitations are not found in claims 1-24 of the present application.



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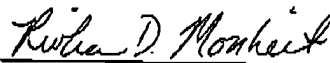
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Therefore, claims 1-24 of the present application are not obvious over claims 1-19 of the copending '728 application.

Allowance of claims 1-26, as amended, is respectfully solicited.

Respectfully submitted,



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